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APPLICATION OF A PORTABLE MICROPROCESSOR-BASED SYSTEM FOR ELECTROPHYSIOLOGICAL FIELD TESTING OF NEUROTOXICITY[1,2]

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16. ABSTRACT

A portable microprocessor-based system designated PEARL II has been developed for neurotoxicity testing in human populations. PEARL II provides a flexible and powerful data acquisition capability to record sensory evoked potentials (auditory, visual and somotosensory), event-related slow potentials (CNV, P300) and behavioral measures. PEARL II has been mounted in a mobile laboratory to facilitate field testing. Data obtained in pediatric lead studies are provided for illustration.

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Abstract

Otto, D., S. Baumann, G. Robinson. Development of A portable microprocessor-based system for electrophysiological field testing of neurotoxicity NEUROBEHAV. TOXICOL. TERATOL. A portable microprocessor-based system designated PEARL II has been developed for neurotoxicity testing in human populations. PEARL II provides a flexible and powerful data acquisition capability to record sensory evoked potentials (auditory, visual and somotosensory), event-related slow potentials (CNV, P300) and behavioral measures. PEARL II has been mounted in a mobile laboratory to facilitate field testing. Data obtained in pediatric lead studies are provided for illustration.

Key Words: sensory evoked potentials, event-related slow potentials neurotoxicity, BAEP, PREP, SEP, CNV, P300, human field testing.

Running Head: Electrophysiological field testing of neurotoxicity

Rationale for Electrophysiological Assessment of Neurotoxicity

The effect of toxicant exposure on nervous system function may be inferred from mood tests or behavioral tests of psychomotor performance, memory and verbal abilities. Direct measures of peripheral and central nervous system function can also be obtained by means of electrophysiological measures of sensory, motor and cognitive function. Compared to behavioral tests, electrophysiological tests are generally more complex to implement, administer and score, and require more elaborate and expensive equipment [1]. On the other hand, many electrophysiological tests require little, if any, verbal mediation or motor skills. These tests are, therefore, essentially "culture-free" and can be administered effectively to infants, pre-verbal children, physically compromised, or even unconscious patients. Under such conditions, electrophysiological measures provide information that cannot be obtained from simpler behavioral measures or clinical examination. Moreover, the availability or several small and portable commercial systems for electrophysiological assessment has made the use of these tests easier and more practical for field studies.

Sensory evoked potential methods have been used widely for neurotoxicity testing in animal models [3,4,14]. Arezzo et al. [1] have reviewed available evidence on the use of evoked potential methods in human neurotoxicity testing. These authors note that EP measures appear to be extremely sensitive to neurotoxicity, but that these measures are not presently feasible for "first line" screening. On the other hand, EP methods have considerable promise for controlled laboratory studies, planned epidemiological studies and clinical evaluation of neurotoxicity in humans.

Application of Endogenous Potentials in Neurotoxicity Testing

Sensory evoked potentials are electrical responses of the brain to external stimuli (auditory, visual or somatosensory) and are thus called exogenous potentials. Internal events or processes initiated in the brain (such as an afferent motor command) also generate electrical potentials that can be recorded on the scalp. These brain waves are called endogenous potentials. If subjects are required to attend, process or respond to external stimuli in some manner such as selectively counting or button pressing when a particular signal occurs, the resultant waveform will include early (sensory-evoked) exogenous components as well as later (cognitive) endogenous components. The term event-related "slow" potentials (ERSPs) refers to later endogenous components associated with information processing, cognition and memory. The latency of endogenous potentials is usually 100 msec or more after stimulus onset. Endogenous potentials may persist for several hundred msec., while exogenous components are usually much briefer. Figure 1 illustrates the temporal and functional characteristics of these two classes of potentials in the auditory modality.

Two prominent ERSPs are: (1) Contingent Negative Variation (CNV), a slow vertex-negative shift in scalp recorded EEG that arises during a signaled reaction-time foreperiod [20] and (2) the P300, a large positive wave that peaks 300-600 msec following a stimulus that delivers relevant information to the perceiver [18].

Although a vast experimental literature has evolved around the CNV and P300 [10,15], the clinical utility of endogenous potentials remains in question. One feature of endogenous potentials that may be useful in neurotoxicological research is that these measures are usually obtained during the performance of sensorimotor or visual tasks. Therefore, changes in behavior and CNS function can be measured concurrently. Endogenous potentials may thus be used to validate behavioral inferences and elaborate neurophysiological effects of toxicant exposure on brain tissue.

Most portable evoked potential systems available commercially are not capable of recording endogenous potentials. More flexible software and additional stimulus generating equipment to create appropriate behavioral contexts are needed to record these potentials in field testing environments. Such a system has been developed for the U.S. Environmental Protection Agency by the Cognitive Psychophysiological Laboratory (CPL) at the University of Illinois. This system has been designated PEARL II (Portable Environmental Assessment and Research Laboratory). Hardware and software features of PEARL II are described elsewhere in this volume [7].

PEARL II Neurotoxicity Test Battery

The test battery currently includes two clinically validated sensory evoked potential tests, the pattern-reversal visual evoked potential (PREP) and brainstem auditory evoked potential (BAEP), and three experimental tests that elicit endogenous potentials during sensory conditioning and target detection tests. We also have the capability to administer nerve conduction velocity and somatosensory evoked potential (SEP) tests. Brief descriptions, examples and comments on measures used in recent studies [13] of children at risk for lead poisoning are presented below.

Brainstem Auditory Evoked Potential. Figure 3 shows BAEPs recorded in five boys with varying blook lead levels. Results of our recent studies [13] suggest that BAEP latencies or interpeak latencies vary systematically with lead exposure history. We have used a binaural BAEP recording obtained from the vertex referred to linked mastoids. Two replicate averages of 2000 trials were obtained with clicks of alternating polarity in order to eliminate stimulus artifact. Clicks were presented at 60 dB above the 2 KHz pure tone threshold obtained from audiometric screening of each subject prior to BAEP recording. A stimulus rate of 11.1 clicks/sec was used to avoid 60 Hz artifact. Latency measures of upward deflections of waves I, III, and V were made. A vertex-positive or mastoid-negative event produced an upward deflection. Central conduction times (I-III, III-V, and I-V interpeak latencies) were calculated for each ear. BAEP testing required 12-15 minutes.

This protocol is fairly simple and rapid to administer, but is not necessarily appropriate for neurotoxicity testing in general. Since the effects of lead on nervous system function appear to be nonspecific, binaural recordings were made. Monaural testing (clicks presented to each ear separately and referred to the insilateral mastoid or ear) would be desirable if more extensive assessment of auditory function were desired, if unilateral effects were expected, or more time were available.

We used a traditional psychophysical approach of determining individual subject's hearing threshold and then presenting clicks at 60 dB above threshold in order to ensure that subjects would be stimulated at equal sensation levels. This apprach is problematic in BAEP testing, however, because the latencies of sequential BAEP components may be differentially sensitive to stimulus intensity. Latency differences due to toxicant

exposure could thus be masked by intensity differences. Wave I, generated in the vicinity of the cochlear nucleus, is most sensitive to hearing (endorgan/deficits). Later waves reflect activity in sequential segments or synapses of the auditory pathway. A preferable approach is to record BAEPs at three different but standard intensities (e.g., 20, 40, and 60 dBHL) for all subjects and to examine the latency-intensity function of wave V latency in exposed vs. control groups. This approach is particularly useful in distinguishing conductive hearing loss from sensorineural hearing loss with recruitment [5]. Hearing thresholds can also be determined electrophysiologically by this method [5]. A disadvantage of this approach for screening is that it takes longer to record at three intensities than at one.

BAEP testing time can be reduced by stimulating at faster rates (e.g., 33-50 clicks per sec). In general, more trials must be averaged at faster rates in order to achieve comparable signal-to-noise resolution. Wave I resolution may also decrease at faster stimulation rates, although Wave V remains robust. Further studies are needed to clarify the optimal stimulus parameters for BAEP testing in toxicant-exposed humans.

Pattern-Reversal Visual Evoked Potentials. Visual acuity of subjects should be determined (e.g., with a standard Snellen eye chart) prior to PREP testing. Subjects who wear glasses should use them during testing to ensure 20/20 acuity. The latency and amplitude of PREP components will be distorted if impaired acuity is not corrected. Subjects must also fixate carefully on the reversing pattern. Conscious or unconscious defocussing will distort the waveform, a problem that is not easy to detect.

Figure 4 shows PREP recorded binocularly from five children with varying lead exposure histories. We predicted that P1 latency would increase directly with lead exposure, but the results were not significant.

We used a full-field presentation of a reversing checkerboard. Twenty-four minute checks were presented at two reversal per second with luminance adjusted to obtain 90 percent contrast of light and dark squares in subdued light.

PREPs were recorded differentially form a mid-occipital (O_z) active electrode and vertex reference electrode. Two hundred trials were averaged to obtain stable binocular waveforms. Two replications were obtained from each subject. Five measures were obtained for each waveform: latencies of N1, P1, and N2 components and peak-to-peak amplitudes of N1P1 and P1N2. For statistical comparisons, the mean of the two replication was used. Visual impairments should yield increased latency and reduced amplitude values. The PREP assessment took about 5 minutes.

The PREP protocol, like the BAEP protocol, is simple and rapid to administer, but its sensitivity and utility in neurotoxicity testing remains to be demonstrated. Monocular testing should be done if unilateral effects are expected and if time is available. Testing at different check sizes and contrast levels might well improve measurement sensitivity. Different types of patters (e.g., sine wave gratings) may be more effective than reversing checkerboards for neurotoxicity testing. PREPs probably cannot be recorded under dark-adapted conditions because the waveform originates primarily in the fovea [17]. If the rods are selectively affected by toxicant exposure, as seems to be the case for several heavy metals [9], other measures sensitive to scotopic vision should be used.

Passive Sensory Conditioning. The passive sensory conditioning task was developed to study the effect of lead exposure on CNS function in young children. Slow potential voltage elicited in children varied systematically with blood lead level (PbB) and age [11]. A similar re-

lationship between slow wave voltage and PbB was observed in a subset of the same children studied two years later, suggesting some persistence of CNS effects despite the fact that PbB levels were considerably lower at the time of follow-up [12]. No significant relationship was found between original PbB and slow wave voltage during passive conditioning in a five-year follow-up study of the same children [13]. Summary averages of slow waves recorded in children during passive conditioning are shown in Fig. 5a. This test takes about 20 min.

Active Sensory Conditioning. Slow potential changes observed in children during passive sensory conditioning are not consistently found in adults. In order to make the test more meaningful for older children and adults, a button-press/reaction-time contingency may be added. In the active sensory conditioning test, subjects are given a button and instructed to press as rapidly as possible when the cartoon is interrupted. The blanking is extended to a maximum of three seconds, but the video returns immediately upon key pressing. Therefore, the subject has operant control over the cartoon interruption. This test is a variant of the foreperiod reaction-time paradigm that is widely used to elicit CNV. Waveforms obtained are similar to those seen in passive conditioning, but the amplitude of the negative portion of the wave is usually greater (Fig. 5). The test takes about 10 min.

Frequent-Rare (Auditory Oddball) Harbin [6] has reviewed the P300 wave and its possible application in neurotoxicity testing. The PEARL II battery contains a prototype test used to elicit the P300. In this paradigm a 100 msec, low pitched tone is presented via loudspeaker (ca. 90 dB SPL) every 1500 msec. A high pitched tone occurs randomly on 25% of the trials. A total of 200 tones are presented consisting of 150

frequent and 50 rare trials. Subjects are instructed to press the button as rapidly as possible when the rare tone occurs, but not to press when the frequent tone occurs. On-line averages of frequent and rare trials are obtained. Single trials are also saved including reaction-time, hit, miss and false alarm data. Editing for eye-blink artifact is not as necessary for this test as it is for sensory conditioning because the tones are presented at a more rapid rate and no blanking of the visual field occurs. Figure 6 shows averaged waveforms obtained during frequent and rare trials in children. This test takes about six min.

Evolution, Application and Evaluation of PEARL II

PEARL II was originally conceived and designed as a system with suitcase portability. As peripheral devices accumulated for display, plotting printing and storage of data, the concept of portability evolved from suitcases to a mobile platform. PEARL II system components were mounted in a large camper adapted for neurotoxicity field testing. The interior of the van contains three sections. The forward section has a small table and is used for subject briefing, collection of questionnaire data and electrode preparation. A small mid-section with chair and stimulus displays is used for visual and cognitive electrophysiological testing. The large aft-section houses most of the data collection, processing and storage equipment as well as a medical examining table that is used for auditory brainstem and somatosensory testing.

The mobile laboratory has been used to collect neurobehavioral data from several different cohorts of children in three North Carolina counties for periods up to five months. These studies of children at risk for lead poisoning have demonstrated that PEARL II is a reliable and effective system for neurotoxicity field testing of human populations. Evidence from

these studies [13,16] has contributed to USEPA's decision to phase-down lead in gasoline, updating the lead criteria document [19], and CDC's recent decision to lower the threshold for undue lead absorption in children [2].

Disadvantages of PEARL II for neurotoxicity field testing include limited assessment capacity (a maximum of six children can be tested daily if auditory, visual and cognitive measures are recorded); the lengthy off-line time required to process cognitive electrophysiology data (an hour or more per subject); lack of standardization of cognitive electrophysiology measures, and the uncertain clinical significance of the latter measures. If assessments were limited to one or two tests, individual testing time could, of course, be reduced substantially. Testing of adults should also be somewhat faster than children.

Based on our experience so far, auditory (BAEP) and visual (PREP) tests appear to be the most useful measures for neurotoxicity assessment. BAEP latency appears to be the most sensitive of the PEARL II measures for assessing the neurobehavioral effects of lead exposure in children [13]. New tests of visual function using sine-wave grating stimuli are currently under development. As microprocessor technology improves and the database grows concerning the sensitivity of event-related brain potentials to neurotoxicant exposure, we anticipate an expanding role for electrophysiological methods in the field testing of human populations exposed to chemical substances.

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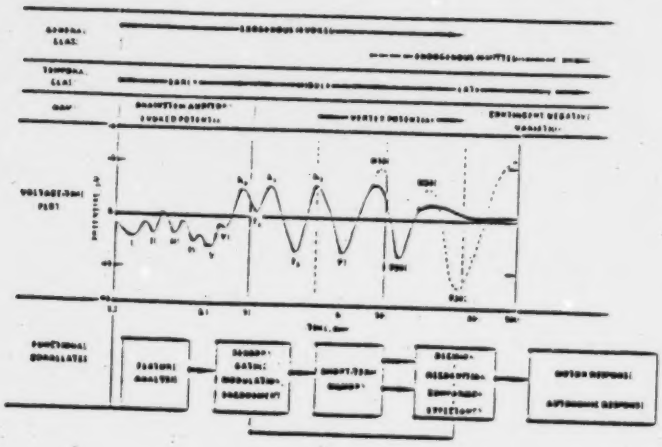
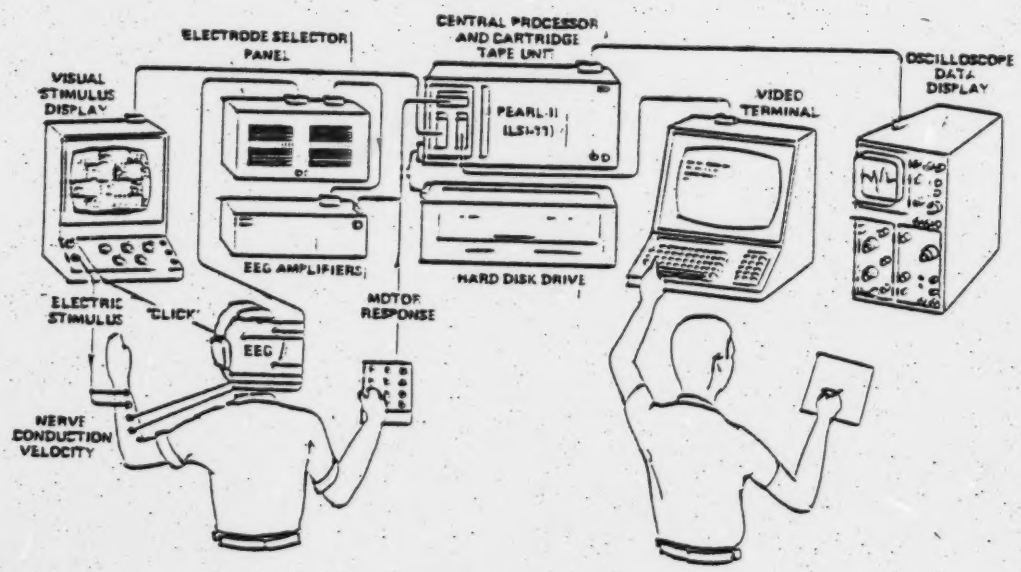
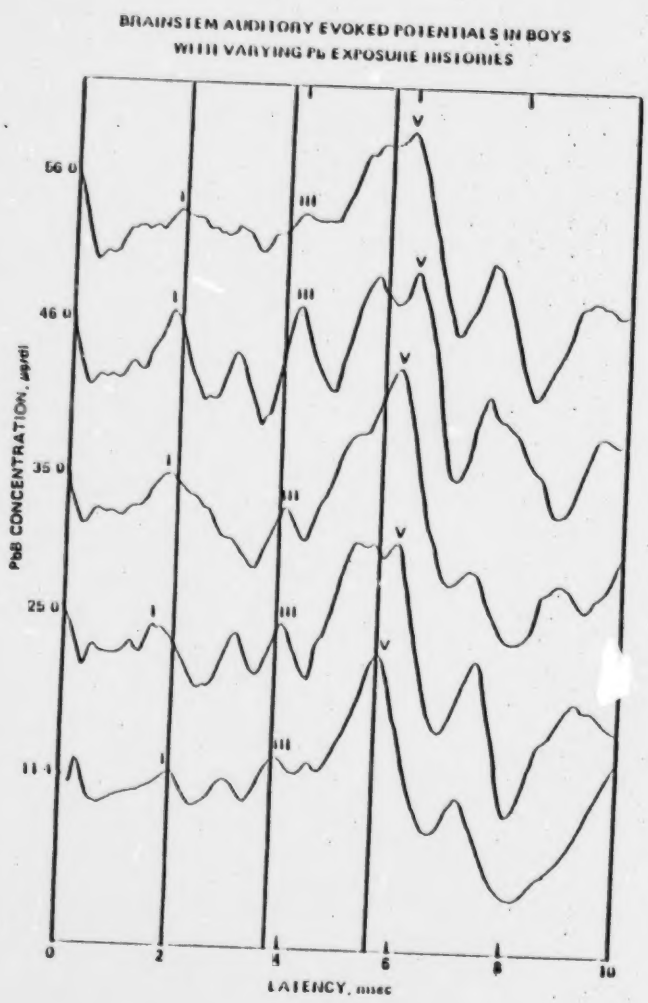


Fig 1



PORTABLE ENVIRONMENTAL ASSESSMENT RESEARCH LABORATORY (PEARL) FOR HUMAN NEUROTOXICITY TESTING

Fig 2


BRAINSTEM AUDITORY EVOKED POTENTIALS IN BOYS
WITH VARYING Pb EXPOSURE HISTORIES
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46.0
35.0
25.0
11.4
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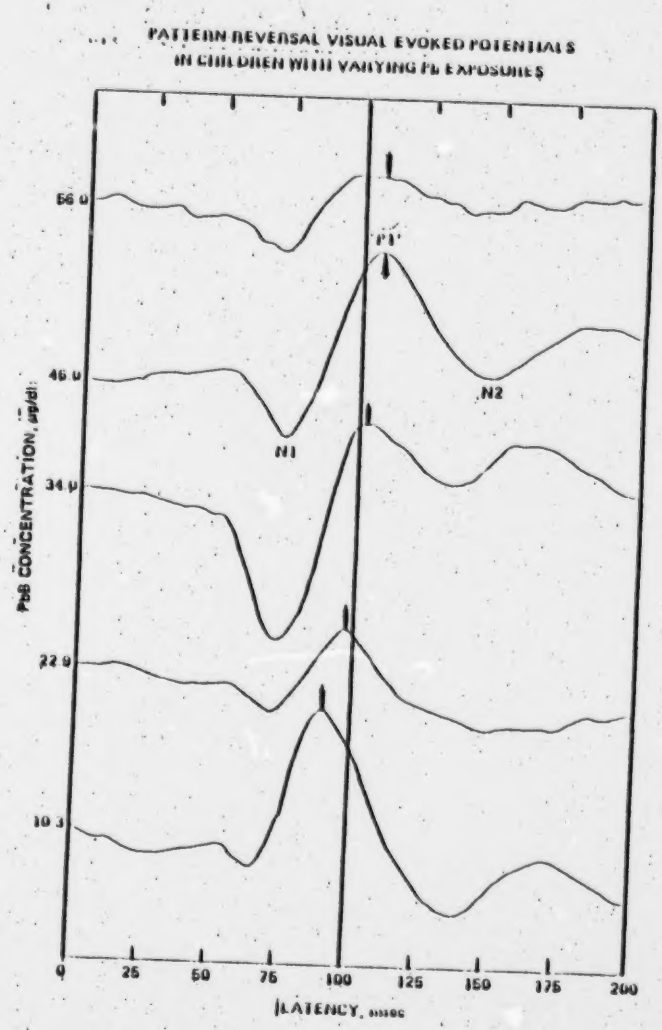
LATENCY, msec

Fig 3


PATTERN REVERSAL VISUAL EVOKED POTENTIALS
IN CHILDREN WITH VARYING Pb EXPOSURES
56.0
46.0
34.0
22.9
10.3
PbB CONCENTRATION, µg/dl
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N1
N2
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175
200
LATENCY, msec

Fig 4

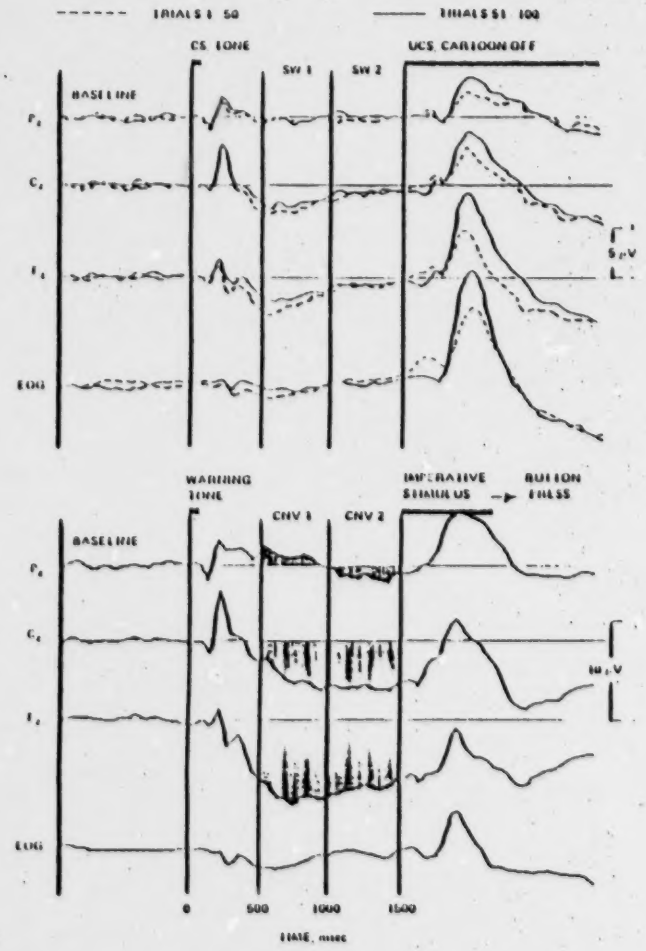
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Fig. 5

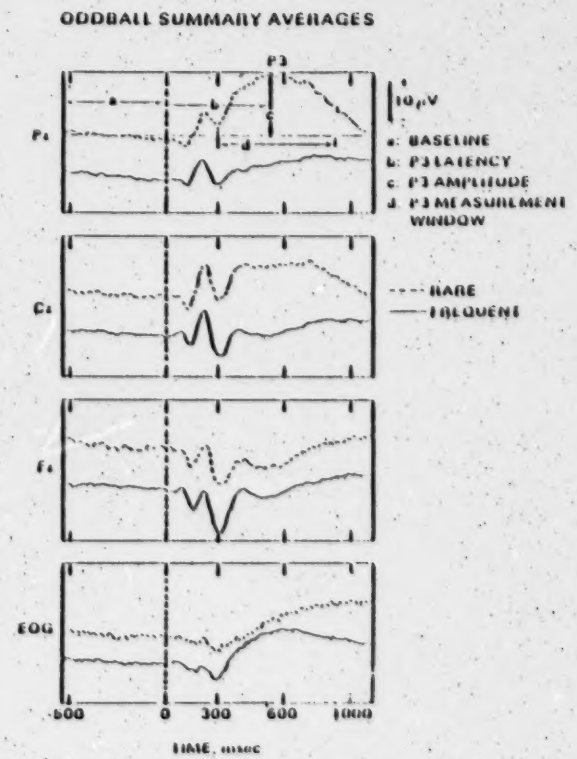
ODDBALL SUMMARY AVERAGES
P3
10 μV
a: BASELINE
b: P3 LATENCY
c: P3 AMPLITUDE
d: P3 MEASUREMENT WINDOW
RARE
FREQUENT
EOG
-500
0
300
600
1000
TIME, msec

Fig. 6